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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/147,490	05/13/1999	FREDERICK A. O. MENDELSOHN	016786/0215	1793

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/147,490	MENDELSOHN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6-9,11-24 and 26-33* is/are pending in the application.

4a) Of the above claim(s) *2,3,6-9,11-17,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-24 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 26 January 2004 has been entered. Claims 2-3, 6-9 and 11-17 were withdrawn by the examiner in the Paper of 30 February 2001. Claims 26 and 27 were withdrawn in the Paper of 17 October 2001. Claims 1, 4, 5, 10 and 25 were cancelled by the applicant in the Paper of 2 August 2001.

The affidavit under 37 CFR 1.132, filed 26 January 2004, is insufficient to overcome the rejection of claims 18-24 and 28-33. Claims 2-3, 6-9 and 11-17 were withdrawn by the examiner in Paper 9 (30 February 2001). Claims 26 and 27 were withdrawn in Paper 13 (17 October 2001). Claims 1, 4, 5, 10 and 25 were cancelled by the applicant in Paper 12 (2 August 2001).

Claims 18-24 and 28-33, with Species 1A ("modifying learning and facilitating memory retrieval") and Species 2A ("dementia") are being examined in this Office Action.

Maintained Objections and/or Rejections

Claim Objections

The objection to Claims 18 and 28 for reciting non-elected subject matter (page 2, 25 August 2003), is *maintained.* Applicants have not amended Claims 18 and 28 to remove recitation of non-elected species.

Claim Rejections

35 *USC § 112, first paragraph - lack of enablement*

Claims 18-24 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, because the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The reasons for this rejection are set forth at pages 3-6 of the previous Office Action (25 August 2003). The specification is not enabling for the limitations of the claims wherein *LVV-Hemorphin* (SEQ ID NO: 1) is used for "modifying learning and facilitating memory retrieval" or for treating "dementia."

Claims 18-24 and 28-33 are drawn to a method of treating a patient or animal with a neuroactive peptide, *LVV-Hemorphin-7* (SEQ ID NO: 1), in order to modulate neuronal activity. Dependent claims recite biological activities such as "modifying learning" and "[treating] dementia" and additional disease conditions, mostly involving neurological conditions. Additional claims recite substitutions of D-amino acids and other amino acid analogs into the *LVV-Hemorphin* peptide.

The specification discloses use of LVV-*Hemorphin-7* to inhibit the amnesia caused by scopolamine in rats. Tests were conducted using passive-avoidance conditioning (Specification, page 28) and acquisition of a water maze map (page 30), both typical methods of testing conditioning and learning in rats. A dose of the acetylcholine antagonist scopolamine immediately before each day's test worsened the performance of the animals in learning shock-avoidance (an example of a passive avoidance test) or in learning a spatial map (e.g., a water maze). Amnesia produced by scopolamine resolved in approximately 24 hours in animals not

given *LVV-Hemorphin-7*. The worsening of test performance in rats was reversed by injection of *LVV-Hemorphin-7* prior to testing.

It is noted that at page 2 of the Response, the Applicant cites pertinent case law reviewing the current legal standards of what constitutes *undue experimentation*. The Examiner takes no issue with the Applicant's general comments regarding the legal standards for the levels of experimentation involved in enablement of novel inventions. Issues specifically pertinent to enablement of the instant invention, however, receive comment below:

Applicants argue (page 3, 26 July 2003) that at the time the application was filed,

"those skilled in the art would have known that the scopolamine model is an accepted model for amnesia, dementia, and other memory related losses in humans and other animals. Thus, the specification enables the modification of a whole range of biological activities in mammals, as presently recited, and not just reversal of temporary, scopolamine-induced memory loss, as the Examiner posits."

Applicants point to the disclosed Declaration (page 3, 26 July 2003) and recited references:

"To evidence what the skilled person knows in the relevant art, applicants provide the declaration of co-inventor Siew Yeen Chai. In paragraph 13 of her declaration, for instance, Dr. Chai points to several instances in the literature that indicate the usefulness of scopolamine as a model for memory-related losses, including amnesia and dementia, in humans as well as other animals. Dr. Chai also identifies studies that illustrate how scopolamine impairs learning and memory under a variety of testing conditions, and how some of these impairments share neuropsychological similarities with impairments attributed to Alzheimer's disease."

Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons:

In general, the Declaration of co-inventor Siew Yeen Chai and the published citations referred to by the Applicants either do not address the issue of enablement of the instant

invention or they specifically contradict the Applicants' contentions that scopolamine administration adequately mimics dementia and related progressive neurological disorders. For example the paper by Gallagher & Rapp (1997, Annual Review of Psychology, Vol. 48, pp. 339-370) does indeed discuss "the importance of animal models for understanding the effects of normal aging on the brain and cognitive functions," but is primarily focused on distinguishing between cognitive dysfunctions caused by disease and those related to aging. Furthermore, their discussion on the use of animal models to study each component of human *aging* as it affects the brain is prefaced by the statement:

The relevance of research with laboratory animals for an understanding of human aging, however, depends on whether the specific functions and biological systems targeted for study are appropriate models for human aging (page 343).

Thus, Gallagher & Rapp's paper is a discussion of the use of animals in studying human *aging*, and even then they seem to advice caution when applying data from animal models. Furthermore, the Enablement rejection of the previous Office Action (25 August 2003) was directed primarily to the use of scopolamine to mimic a permanent neurological condition, not the fact that scopolamine was administered to animals *per se*; the same arguments could be made if scopolamine had been injected into normal humans. In other papers submitted with the response of 26 January 2004, researchers have argued *against* the use of scopolamine for modeling dementia. For example, Molchan, et al, (1992, Brain Res. Rev., 17: 215-226) points out specifically that scopolamine is a poor model for dementia:

The effects of scopolamine have been inconsistent on measures of retrieval from knowledge memory among different studies. The lack of an effect on such measures has been one

of the primary arguments against the scopolamine model of dementia, as patients with AD are substantially impaired in retrieval from knowledge memory (page 223, section 5.3).

The authors continue:

Any model, especially of something as complicated as memory impairment, will have limitations. It is unrealistic to think that transient deficits secondary to acute drug challenge will precisely model changes in cognitive functioning that occur over a long period of time. Further complicating matters, neurotransmitter deficits other than those in the cholinergic system occur in AD and probably contribute to the memory and other cognitive impairments in the disease (page 223, section 5.4).

Other papers submitted with the Applicants' response discuss the contribution of acetylcholine and cholinergic neurons in dementia and in learning and memory (Blokland, et al, 1995, Brain Res Rev., 21(3): 285-300; Isacson et al, 2002, Trends in Neuroscience 25(2): 79-84; Davies P, & Maloney A, 1976, Lancet, Letters to the Editor, p. 1403; Naveen & Kohli, 2003, Indian Joumal of Pharmacology, 35: 104-108; Ye et al, 1999, Journal of Pharmacol. Exp Ther; 288(2): 814-819; and, Ebert & Kirch, 1998, European Journal of Clinical Investigation, Volume 28 Issue 11, page 944). The current literature, in general, underscores the importance of cholinergic neurons in the cortex and hippocampus in memory processing and in disease states such as Alzheimer's disease. As cited in the Declaration of Dr. Chai (paragraph 9):

Acetylcholine is a neurotransmitter that plays an important role in processing learning and memory and therefore its breakdown disrupts nerve communication in the brain, which causes cognitive decline and other memory problems.

Indeed, Applicants have shown that acetylcholine is very important for acquisition of

conditioned responses in their experimental animals, as well as for short-term memory processing in normal animals- and no doubt humans- since administration of scopolamine causes a condition whereby consolidation of working memory is temporarily disrupted (see Specification, Figure 14, for example).

However, Applicants have not provided anything but a weak nexus between scopolamine-induced amnesia and long-lasting memory impairments such as dementia. A drug-induced condition that "cures itself" in approximately 24 hours and leaves no residual cognitive impairments does not appear to be a good model for a complicated and relentlessly destructive disease such as Alzheimer's disease, as discussed above.

As noted in the Declaration sent 26 January 2004, the recited ligand *LVV-Hemorphin-7* (SEQ ID NO: 1) is an angiotensin receptor ligand (Lee, et al, 2003, J. Pharmacol. Exp. Therap, 305: 205-211), and not a scopolamine inhibitor, as recited by the Examiner.

Proper analysis of the Wands factors were provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine how to use *LVV-Hemorphin-7* to ameliorate a neurodegenerative disorder or facilitate learning and memory; the lack of direction or guidance in the specification regarding the same; the lack of working examples in which *LVV-Hemorphin-7* was used to treat a complex disorder related to neuronal activity; the state of the art showing the complexities of neurodegenerative disorders; and the breadth of the claims which embrace many types of central nervous system disorders, --undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

35 U.S.C. 112, first paragraph- Written Description

The rejection of Claims 30-33 under 35 U.S.C. 112, first paragraph, for lack of Written Description is *maintained.* This rejection was made at pages 6-7 of the previous Office Action (25 August 2003), because the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants argue (26 January 2004) that if the Specification teaches *how* to make the variants of SEQ ID NO: 1 and provides background to the proposed mutations, the written Description requirement will be satisfied. However, Claims 30-33 are directed to methods of using SEQ ID NO: 1 (a peptide of ten amino acids) when it encompasses an *unknown number* of polypeptides, and comprising proposed mutations that would result in substitution or deletion of processing sites on the ligand polypeptide, the results of which would be unexpected.

The specification teaches *LVV-Hemorphin-7* (SEQ ID NO: 1). However, the specification does not teach functional or structural characteristics of all possible *LVV-Hemorphin-7* polypeptides encompassed by the claims. The description of one *LVV-Hemorphin-7* polypeptide species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polypeptides. Applicants have not made and tested all possible encompassed variants of SEQ ID NO: 1 in the described behavioral tests, nor even tested a representative subset of possible encompassed variants of SEQ ID NO: 1.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is

703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
5/13/04

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER